REMARKS

Status of the Claims

Claims 1-13, 16, and 18-22 are pending in the present application. Claims 14 and 17 were previously canceled. Claims 15 and 23 are presently canceled. Claims 1-11 and 18-21 are withdrawn as directed to a non-elected invention. Claims 11, 16, and 22 are amended.

As amended, the CNP derivatives described in claims 11 and 22 are supported throughout the application as originally filed. Support for the CNP-22 analogs encompassed by the present claims is found, *e.g.*, on page 12, lines 26-29 to page 13, line 19, in the originally filed application. For example, page 12 of the originally filed application states that the amino acid sequences on page 13, which are set forth as SEQ ID NOS: 3 to 10 in the present application, describe CNP-22 analogous peptides.

The CNP-53 analogs encompassed by claims 11 and 22 are also supported by the originally filed application. For example, page 13, lines 18-19 specify that "[e]xamples of CNP-53 analogous peptides include cyclic peptides comprising amino acid variations similar to those of the CNP-22 analogous peptides." Applicants submit that it is clear from the instant application that CNP-22 analogous peptides refer to the peptides of SEQ ID NOS: 3 to 10. Applicants further submit that the originally filed application indicates that CNP-53 analogs, which are "similar to those of the CNP-22 analogous peptides" comprise the amino acid sequences of SEQ ID NOS: 3 to 10. Accordingly, the originally filed application supports that the CNP-53 analogs encompassed by the present claims are derived from CNP-53 by substituting the 32-53 amino acids of CNP-53 (that is, Gly^{32}, Leu Ser...Leu Gly Cys^{53} of SEQ ID NO: 2) by any of the amino acid sequences of SEQ ID NOS: 3 to 10.

Applicants further submit that it is also clear from the present application that the CNP-22 analogs retain CNP activities, as determined by a cGMP assay. For example, the present application teaches on page 12, lines 26-29 that the CNP-22 analogous peptides are described in Japanese Patent Publication No. 6-9688 A (1994). As noted in the response submitted on January 22, 2010, JP 6-9688A (1993) corresponds to U.S. Patent No. 5,434,133. JP 6-9688 A also corresponds to EP No. 0 497 368 A1. U.S. Patent No. 5,434,133 is clearly equivalent to JP 6-9688 A as evident by the Foreign Priority Data, which describes JP 3-011321 and JP 3-254066, which is an application number of published Japanese Application No. JP 6-9688 A, *see also* Family Status Legal Report for U.S. Patent No. 5,434,133, *enclosed*, and EP 0 497 368 A1.

For the Examiner's consideration, Applicants submit herewith EP 0 497 368 A1, which is a complete translation of corresponding Japanese Patent Publication No. 6-9688 A.

Applicants further submit that CNP activity is defined in the originally filed application. *See*, for example, page 12, lines 19-25.

Claim 11 is also amended to correct antecedent basis and to remove superfluous punctuation. In particular, the comma between "fibroblast growth factor receptor 3" and "(FGFR3)" is deleted from claim 11. Claim 16 is amended for clarity. Claim 22 is amended according to the Examiner's recommendation on page 9 of the instant Office Action. No new matter has been entered by way of this amendment. Reconsideration is respectfully requested.

Amendments to the Specification

As noted above, the specification is amended to cancel the subject matter, which the Examiner asserts is not supported by the present application in an effort to expedite prosecution. No new matter is entered by way of this amendment. Reconsideration is respectfully requested.

Maintained Objections and Rejections

Claim Objections

The Examiner objects to claim 11 for the phrase "a body height of an individual", *see* Office Action, page 3. This phrase is amended to specify "the body height of an individual" per the Examiner's suggestion. Accordingly, the objection is overcome and withdrawal is respectfully requested.

Issues under 35 U.S.C. § 112, First Paragraph

Enablement

Claims 11-13, 15, 16, 22, and 23 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement, *see* Office Action, pages 3-7. Applicants respectfully traverse.

Basis for the Rejection

Specifically, the Examiner maintains that the claims encompass any "derivative" of CNP. The Examiner further asserts that the term "C-type natriuretic peptide (CNP)" broadly encompasses "a derivative" of CNP. Accordingly, the Examiner believes that the claims specify

a genus that is broader in scope than either "a CNP of SEQ ID NO: 1 or 2" or "a mammalian or avian C-type natriuretic peptide", *see* Office Action, page 5.

The present invention

Independent claim 11 is directed to a method for increasing the body height of an individual free from fibroblast growth factor receptor 3 (FGFR3) abnormality, comprising administering systemically C-type natriuretic peptide (CNP) or a derivative thereof to increase the body height in the individual, wherein the individual has growth cartilage layers, wherein the CNP is CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2, wherein the derivative is selected from the group consisting of: CNP derivatives set forth as SEQ ID NOS: 3 to 10; and CNP derivatives which are obtained from the amino acid sequence of SEQ ID NO: 2 by substituting the 32-53 amino acids thereof by any of the amino acid sequences of SEQ ID NOS: 3 to 10, wherein the CNP derivatives possess a CNP activity.

Independent claim 22 is directed to a method for extending a cartilage bone free from FGFR3 abnormality in an individual, comprising administering systemically-type natriuretic peptide (CNP) or a derivative thereof to activate guanyl cyclase B (GC-B) in the individual, wherein the individual has growth cartilage layers, wherein the CNP is CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2, wherein the derivative is selected from the group consisting of: CNP derivatives set forth as SEQ ID NOS: 3 to 10; and CNP derivatives which are obtained from the amino acid sequence of SEQ ID NO: 2 by substituting the 32-53 amino acids thereof by any of the amino acid sequences of SEQ ID NOS: 3 to 10, wherein the CNP derivatives possess a CNP activity.

The instant claims are enabled by the specification

As noted above, the amended claims specify that CNP is CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2. The CNP derivatives in the amended claims are limited to CNP-22 analogs of SEQ ID NOS: 3 to 10 and CNP-53 analogs, which are obtained by substituting amino acids 32-53 of CNP-53 by any of the amino acid sequences set forth in SEQ ID NOS: 3 to 10. Also as noted above, all of the CNP analogs are supported by the originally filed application.

In view of the foregoing amendment, Applicants submit that the amended claims comply with the enablement requirement. Withdrawal of the rejection is respectfully requested.

Written Description

Claims 11-13, 15, 16, 22, and 23 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see* Office Action, pages 7-8. Specifically, the Examiner states that the claims encompass any derivative of CNP. Applicants respectfully traverse.

As noted above, the amended claims describe particular derivatives of CNP. Specifically, the amended claims encompass CNP derivatives, which are the CNP-22 analogs of SEQ ID NOS: 3 to 10, and CNP-53 analogs, which are obtained from CNP-53 by substituting the 32-53 amino acids of CNP-53 by any of the amino acid sequences of SEQ ID NOS: 3 to 10. Accordingly, the CNP and the CNP derivatives thereof are within the scope of the disclosure of the originally filed specification. In view of the foregoing, an ordinary artisan would have recognized that Applicants were in possession of the invention at the time of filing. Withdrawal of the rejection is respectfully requested.

New Objections and Rejections

Object to the Specification

The Examiner objects to the specification because the specification states that International Publication No. WO 02/074234 corresponds to U.S. Patent No. 5,434,133, *see* Office Action, pages 8-9. However, the Examiner states that Applicants have failed to provide evidence of the correspondence between the International Publication and the Patent.

As described above, the specification is amended to cancel the subject matter to which the Examiner objects. Accordingly, the rejection is moot and withdrawal is respectfully requested.

Claim Objections

Claims 11 and 22 are objected to for the reasons set forth on page 9 of the instant Office Action. Applicants respectfully traverse.

As noted above, the claims are amended. In view of the amendments, Applicants believe the objections are obviated and respectfully request withdrawal.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 11-13, 15, 16, 22, and 23 are rejected as allegedly indefinite, *see* Office Action, pages 9-10. Applicants respectfully traverse.

Applicants submit that the subject matter, which the Examiner states is unclear on page 9 and page 10 at lines 1-6 of the instant Office Action is canceled. Accordingly, this aspect of the rejection is moot.

The Examiner asserts that the term "CNP" on line 1 of claims 15 and 16 is not clear in terms of antecedent basis because two "CNPs" are described, *i.e.*, on lines 3 and 7 of claim 11.

In this regard, claim 15 is cancelled, and in claim 16 the term "the CNP" is amended to specify "the CNP or the derivative thereof." Accordingly, Applicants submit that the antecedent basis is clear and request withdrawal of the rejection.

Issues Under 35 USC 112, First Paragraph, New Matter

Claims 11-13, 15, 16, 22, and 23 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter, *see* Office Action, pages 10-12. Applicants respectfully traverse.

Claims 15 and 23 are canceled. Accordingly, the rejection is moot in regard to these claims. As noted above, Applicants submit that claims 11 and 22 are amended to restrict CNP and derivatives thereof as described in the claims to those disclosed in the originally filed application. Also, as noted above, Applicants submit that the CNP-22 analogs described in the instant claims are based upon the disclosures of JP 6-9688 A (1994) and WO 02/074234. As further described above, Applicants submit that U.S. Patent No. 5,434,133 corresponds to JP 6-9688 A, *see* the priority data described in U.S. Patent No. 5,434,133. For the Examiner's reference, enclosed is a copy of EP 0 497 368 A1, which is a complete translation of JP 6-9688 A. In view of the foregoing, Applicants believe this rejection is overcome and respectfully request withdrawal.

Issues under 35 U.S.C. § 103(a)

Claims 11-13, 15, 16, 22 and 23 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable Miyazawa *et al.*, 2002, *Endocrinology* 143(9):3604-3610 ("Miyazawa") and in view of Suda *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1998, 95:2337-2342, ("Suda"), *see* Office Action, pages 12-16. Applicants respectfully traverse.

When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *International v. Teleflex Inc.*, 82 USPQ2d 1385 (2007).

Initially, Applicants note that Miyazawa teaches a transgenic (Tg) mouse, with targeted expression of CNP in the growth plate chondrocytes under the control of the mouse pro-α1(II) collagen (Col2a1) promoter. The Tg mouse was generated by the method described in H. Chusho *et al.*, ("Dwarfism and early death in mice lacking C-type natriuretic peptide," *Proc. Natl. Acad. Sci.*, March 27, 2001, vol. 98, no. 7, pp. 4016-4021), *enclosed*. The Tg mouse was prepared such that the CNP was specifically expressed solely in the growth plate chondrocytes. This CNP expression is evident from the phrase "targeted expression of CNP", *see* Office Action, page 14. This CNP expression is also clearly described by Chusho, *i.e.*, "the transgene expressed was detected only in the chondrocytes", *see* page 4016, second column of Chusho *et al.* In view of the foregoing, CNP expression in the Tg mouse as described by Miyazawa, was confirmed only in chondrocytes. This description of CNP expression is different from systemic administration. Hence, the Examiner's assertion, *i.e.* "Miyazawa teach a method comprising administering systemically C-type natriuretic (CNP) in an individual without a FGRF3 mutation and with growth cartilage layers," is NOT correct.

The Examiner further asserts that it would have been obvious to a person of ordinary skill in the art to substitute the human serum amyloid-P component promoter used by Suda for the mouse pro-α1(II) collagen (Col2a1) promoter in the transgenic mice disclosed by Miyazawa, thus creating a CNP-transgenic mouse wherein CNP is expressed in the plasma rather than locally in the collagen.

As also pointed out by the examiner, Suda teaches that: (i) transgenic mice with elevated plasma BNP concentrations exhibit deformation and elongation of bones; (ii) CNP increases the total longitudinal bone growth and cGMP production in cultured embryonic mouse tibias more

potently than BNP, strongly suggesting that activation of chondrogenesis by NP is mediated primarily via GC-B; and (iii) it is tempting to speculate that CNP is the endogenous ligand for GC-B in the bone *in vivo*.

Applicants submit that the Examiner's assertion is focused on speculating a relationship between CNP and GC-B, and does not provide motivation for systemically administering CNP. As described in Y. Tawaragi *et al.*, ("Gene and Precursor Structures of Human C-Type Natriuretic Peptide," *Biochemical and Biophysical Research Communications*, March 15, 1991, vol. 175, no. 2, pp. 645-651), and M. Kojima *et al.*, ("Cloning and sequence analysis of a cDNA encoding a precursor for rat C-type natriuretic peptide (CNP)," *FEBS Lett.*, December 1990, vol. 276, no. 1,2, pp. 209-213) *enclosed*, BNP is mainly produced in the heart and serves as a hormone peptide secreted into blood plasma from heart. CNP, in contrast, is exclusively produced in brain. Accordingly, CNP is a molecule different from ANP or BNP. These facts were known at the filing date of this application.

In view of the foregoing, even if BNP, which is secreted into blood plasma to serve as a hormone, could enhance its activity by systemic administration, it would have been difficult for an ordinary artisan at the time of the invention to have reasonably predicted whether or not CNP exhibits similar effects both *in vivo* and *in vitro* when CNP, which expresses specifically in brain, is administered. Furthermore, an ordinary artisan could not have reasonably predicted the effects which are obtained when the concentration of CNP in blood plasma is elevated by systemic administration, rather than by local administration.

In view of the foregoing, an ordinary artisan could not have reasonably predicted the advantages of the claimed invention from the combination of Miyazawa and Suda. Further, Suda does not provide any motivation to systemically administering CNP. Accordingly, the claims are not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants believe the present application is in condition for allowance. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046 at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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Attachments